DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 341

DMB Display Date 12-20-02
Publication Date 12-23-02
Certifier R. LEDESMA

[Docket No. 76N–052G]

RIN 0910–AA01

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-The-Counter Human Use; Final Monograph for Combination Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph that establishes conditions under which over-the-counter (OTC) cold, cough, allergy, bronchodilator, and antiasthmatic (cough-cold) combination drug products are generally recognized as safe and effective and not misbranded as part of its ongoing review of OTC drug products. FDA is issuing this final rule after considering public comments on the agency's proposed regulation (tentative final monograph) and new data and information on OTC cough-cold combination drug products that have come to the agency's attention.

DATES: This regulation is effective [*insert date 24 months after date of publication in the* **Federal Register**].

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of September 9, 1976 (41 FR 38312), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products, together with the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel), which was the advisory review panel that evaluated these products. The agency's proposed regulation for OTC cough-cold combination drug products was published in the **Federal Register** of August 12, 1988 (53 FR 30522).

Final rules for these OTC drug products were published in segments: Anticholinergic (50 FR 46582, November 8, 1985), bronchodilator (51 FR 35326, October 2, 1986), antitussive (52 FR 30042, August 12, 1987), expectorant (54 FR 8494, February 28, 1989), antihistamine (57 FR 58356, December 9, 1992), and nasal decongestant (59 FR 43386, August 23, 1994). This document on combination drug products, general issues, and miscellaneous ingredients is the final segment. In response to the proposed rule for OTC cough-cold combination drug products, the agency received 21 comments, which are on public display in the Dockets Management Branch, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. This final monograph addresses all comments and objections, except as discussed below.

In the **Federal Register** of July 27, 1995 (60 FR 38636), FDA published a final rule establishing that cough-cold combination drug products containing theophylline are not generally recognized as safe and effective and are

misbranded for OTC use. In the **Federal Register** of September 27, 2001 (66 FR 49276), FDA published a partial final rule for cough-cold combination drug products containing a bronchodilator, stating that combinations containing any oral bronchodilator and any analgesic(s) or analgesic-antipyretic(s), anticholinergic, antihistamine, oral antitussive, or stimulant active ingredient are not generally recognized as safe and effective and are misbranded for OTC use. The combinations in these two final rules are listed in § 310.545(a)(6)(iv)(B) and (a)(6)(iv)(D), respectively (21 CFR 310.545(a)(6)(iv)(B) and (a)(6)(iv)(D)).

This final rule does not address the combination of an oral bronchodilator and an expectorant or the combination of an oral bronchodilator and an oral nasal decongestant, which had not been previously classified. These two combination products will be addressed in a future issue of the **Federal Register.**

In the tentative final monograph for OTC cough-cold combination drug products, the agency proposed that combinations containing promethazine hydrochloride be switched from prescription to OTC status for short-term use (7 days) for relief of symptoms of the common cold (53 FR 30522 at 30559). In response, the agency received a citizen petition from a consumer's group and comments from several physicians objecting to OTC status for promethazine-containing drug products. The major concern raised was that use of promethazine in children under 2 years may be associated with the occurrence of sudden infant death syndrome, and that OTC availability could "dramatically increase" its "overuse" in children this age. The petition also raised concerns about possible adverse neurological reactions with promethazine. Following discussion at a Pulmonary-Allergy Drugs Advisory

Committee meeting on July 31, 1989, the agency announced that cough-cold drug products containing promethazine hydrochloride could not be marketed OTC under the monograph (54 FR 36762, September 5, 1989). Subsequently, the agency received additional data to support OTC status for promethazine combinations for relief of symptoms of the common cold (Refs. 1, 2, and 3). The agency has not completed its review of these data nor made a final decision at this time on OTC use of promethazine combinations for relief of symptoms of the common cold and will issue a final decision in a future issue of the **Federal Register**.

In the **Federal Register** of April 9, 1996 (61 FR 15700), the agency published a final rule/enforcement policy establishing § 341.70 (21 CFR 341.70) for the use of diphenhydramine citrate and diphenhydramine hydrochloride as an antihistamine and an antitussive for treating concurrent symptoms in either a single-ingredient or combination drug product. That final rule permitted OTC marketing of such products pending completion of the current final rule.

Some of the combinations in this final rule include cough-cold ingredients in combination with either systemic analgesic-antipyretic or topical oral anesthetic/analgesic and demulcent ingredients. The monographs for these OTC drug products have not been finalized to date. Topical oral analgesic-antipyretic active ingredients were proposed in part 343 (21 CFR part 343) in the tentative final monograph for OTC internal analgesic, antipyretic, and antirheumatic drug products (53 FR 46204, November 16, 1988). Anesthetic/ analgesic and demulcent active ingredients were proposed in part 356 (21 CFR part 356) in the tentative final monograph for OTC oral health care drug products (53 FR 2436, January 27, 1988, and amended at 56 FR 48302,

September 24, 1991). The citations to parts 343 and 356 in this final rule refer to the proposed sections that appear in the tentative final monographs. When the final monographs are issued for those two classes of OTC drugs, crossreferences to applicable sections will be included in part 341 (21 CFR part 341). If any changes occur in the monograph conditions in those tentative final monographs, they will be stated in the final monographs and any appropriate revisions that may need to be made in part 341 will also be stated in those final rules.

The agency advises that on or after [*insert date 24 months after date of publication in the* **Federal Register**], no OTC drug product that is subject to this monograph and that contains a nonmonograph condition may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application or abbreviated application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily as soon as possible.

II. The Agency's Conclusions on the Comments

A. General Comments on Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products

(Comment 1) One comment noted a possible conflict between the use of the terms "should" in proposed § 341.85(b)(1) and (b)(2) (which state: "The following indication for analgesic-antipyretic ingredients should be used") and "must" in proposed § 341.85(b)(3) (which states: "Both indications in § 341.85(b)(1) and (2) must be used."). The comment requested clarification

of the agency's intention and the impact on the "flexibility" policy in § 330.1(c)(2) (21 CFR 330.1(c)(2)).

The agency notes that the word "should" was used in proposed § 341.85(b)(1) and (b)(2) to reflect the flexibility policy set forth in § 330.1(c)(2) that is mentioned in the introductory paragraph under § 341.85(b). The word "must" in proposed § 341.85(b)(3) indicated that both of the indications specified in § 341.85(b)(1) and (b)(2) are required when a manufacturer elects to make both claims for its product. Although the words "should" and "must" are not used in this final rule, when both claims appear in labeling, the exact wording in § 341.85(b)(1) and (b)(2) need not be used because alternate wording in accord with § 330.1(c)(2) may be used.

B. General Comments on Miscellaneous OTC Ingredients

(Comment 2) One comment submitted published literature (Ref. 4) to support the effectiveness of ascorbic acid (vitamin C), which was classified in category III in the tentative final monograph (53 FR 30522 at 30529), to reduce the duration and symptoms of the common cold. The comment contended that, although ascorbic acid may not prevent the common cold, there is considerable evidence indicating it is beneficial in reducing the duration and unpleasant symptoms of the common cold. The comment also submitted an unpublished study (Ref. 5) on the preventive effects of 500 milligrams (mg) ascorbic acid taken four times a day against naturally transmitted rhinovirus 16 in college students under strictly controlled conditions. The comment contended that preliminary results from this study show significant beneficial effects for several cold symptoms, such as cough.

The agency has determined that the submitted studies do not contain sufficient detail to assess their value in establishing the effectiveness of

ascorbic acid in reducing the duration or symptoms of the common cold. In 1990, the agency asked the author of the comment to provide additional information (Ref. 6): (1) A detailed critical appraisal of these studies in accordance with the content and format described in § 314.50(d)(5) and (d)(6) (21 CFR 314.50(d)(5) and (d)(6)) (for clinical data and statistical analysis); and (2) a full report, including the protocol, complete patient data, and statistical analysis, of the rhinovirus study. This information was never provided. Thus, the agency is not including ascorbic acid in this final monograph.

(Comment 3) One comment noted the American Academy of Pediatrics' (AAP) recommendation for safety closures for products with over 5 percent ethanol (volume/volume (v/v)) (53 FR 30522 at 30529). The comment said the statutory authority to require child-resistant closures rests with the Consumer Product Safety Commission (CPSC) under the Poison Prevention Packaging Act of 1970, as mentioned in the tentative final monograph (53 FR 30522 at 30527). The agency notes that CPSC has published a final rule requiring child-resistant packaging for mouthwashes with 3 grams (g) or more of absolute ethanol per package (60 FR 4536, January 24, 1995).

(Comment 4) One comment argued against the AAP recommendations to limit the alcohol content of cough-cold drug products not intended for use in households with children or not labeled for use in the pediatric population. (See cough-cold combination tentative final monograph, comment no. 16 (53 FR 30522 at 30528 to 30529).)

The agency published a final rule for OTC drug products intended for oral ingestion that contain alcohol in the **Federal Register** of March 13, 1995 (60 FR 13590). In § 328.10 (21 CFR 328.10), the agency established the following alcohol limitations in OTC drug products: (1) A 10-percent alcohol limit for

OTC drug products intended for adults and children 12 years of age and over, (2) a 5-percent alcohol limit for OTC drug products intended for children 6 to under 12 years of age, and (3) an 0.5-percent alcohol limit for OTC drug products intended for children under 6 years of age. That final rule was effective on March 13, 1996.

(Comment 5) One comment responded to the agency's request in comment no. 14 of the tentative final monograph (53 FR 30522 at 30528) for information on the minimum concentration of menthol needed to achieve a: (1) Flavoring effect and (2) therapeutic effect. The comment stated that menthol is generally recognized as safe for use as a flavoring substance in the food additive regulations (§§ 172.515 and 182.20 (21 CFR 172.515 and 182.20)); there are no numerical minimum or maximum concentrations; and the only regulatory condition is that flavoring substances be used in the minimum quantity needed to produce their intended effect, which the comment defined as the desired organoleptic impact that achieves consumer acceptance of the product. The comment argued the same principle should apply to OTC drug products containing menthol as a flavoring agent.

With respect to the minimum amount of menthol needed to achieve a therapeutic effect, the comment stated that the oral health care drug products tentative final monograph provides for topical oral anesthetic/analgesic use in a solid dosage form at a dose of 2 to 20 mg every 2 hours as needed (56 FR 48302 at 48344) and the antitussive drug products final monograph provides for a solid dosage form at a dose of 5 to 10 mg every hour as needed (52 FR 30042 at 30056). The comment concluded that the distinction between menthol as a flavoring and therapeutic agent should be based on the types of claims that are made for menthol in product labeling. The comment contended that

this approach may include the dual use of menthol as an active ingredient and as a flavor in the same product with appropriate claims for each use on the product label.

The agency stated in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30528) that if menthol is present at a therapeutic level in a product, it is considered an active ingredient in that product. Menthol is an OTC topical antitussive (§ 341.14(b)(2)) with a dosage in a lozenge of 5 to 10 mg every hour as needed (§ 341.74(d)(2)(iii)). Combinations containing menthol used topically as an antitussive are included in § 341.40 of this final monograph provided that the product is available in a solid dosage form to be dissolved in the mouth (see section I.D, comment no. 12 of this document). Menthol is also proposed as a topical oral anesthetic/analgesic in a solid dosage form in § 356.12(f) with a dosage of 2 to 20 mg every 2 hours as needed (proposed § 356.52(d)(6)(ii), 56 FR 48302 at 48344). Proposed § 356.26(a) through (e) (56 FR 48343) for topical oral anesthetic/analgesics include the combinations containing menthol with a dosage of 2 to 20 mg every 2 hours. If menthol were used only as a flavor in any of these antitussive or anesthetic/analgesic products, then it must be used at an amount less than the minimum dosage for the product's indication(s); otherwise it would be deemed to be present in the product at a therapeutic level and would be considered active.

Section 172.515 of the food regulations states that flavoring substances and adjuvants may be safely used in foods when "they are used in the minimum quantity required to produce their intended effect." Similarly, when menthol is used in OTC drug products as an inactive ingredient for flavoring purposes, the minimum quantity needed to produce the intended effect should be used.

Use should also be in accord with § 330.1(e) (21 CFR 330.1(e)), i.e., the inactive ingredient is safe in the amount administered and does not interfere with the effectiveness of the drug product or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity.

Because there is an effective dosage range, it is possible that menthol could be present in an antitussive or anesthetic/analgesic drug product both as an active ingredient and as a flavor. In such a situation, the agency would consider all of the menthol present to be an active ingredient, and menthol should be listed in the product's labeling as an active ingredient. However, the product could still state in its labeling that it is menthol flavored. In either case (antitussive or anesthetic/analgesic drug product), the total amount of menthol in the product cannot exceed the upper dosage limit stated in either monograph based on the product's labeled use(s).

(Comment 6) One comment requested clarification of the acceptable level of turpentine oil as an inactive ingredient in an ointment combination product applied topically to the chest as an antitussive. The comment stated that the agency did not consider turpentine oil to be an inactive ingredient because of its high concentration (4.7 percent weight/weight (w/w)) in the product (53 FR 30522 at 30550) and had previously indicated that 2 percent w/w was an acceptable level for turpentine oil as an inactive ingredient in the product (Ref. 7).

As the comment noted, the agency previously reviewed this matter (Refs. 7, 8, and 9) and determined that 2 percent or less w/w was an acceptable level of turpentine oil as an inactive ingredient in these ointment products. This use of turpentine oil as an inactive ingredient, e.g., as a fragrance or for tactile

properties, in these OTC drug products should be in the minimum quantity needed to produce the intended effect.

C. General Comments on OTC Cough-Cold Combination Drug Products

(Comment 7) One comment referred to comment no. 60 in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30550), concerning "irreconcilable" pediatric dosages for OTC cough-cold/ internal analgesic-antipyretic combinations. Referencing the agency's notice of intent on pediatric dosing information for OTC drug products (53 FR 23180, June 20, 1988), the comment asked the agency to consider both weight-related and age-related pediatric dosage ranges for ingredients in OTC cough-cold combination drug products in that rulemaking.

The agency intends to address pediatric dosing issues for OTC cough-cold/ internal analgesic-antipyretic combination drug products in a future issue of the **Federal Register**. For OTC cough-cold combination drug products containing oral analgesic-antipyretic active ingredients, this final rule applies only to the directions for adults and children 12 years of age and over; the directions for children under 12 years of age are deferred and do not need to conform to the directions in part 341 at this time.

(Comment 8) One comment mentioned an earlier request that the effective date for reformulation and relabeling of combination drug products containing ingredients from more than one monograph be the effective date of the last applicable final monograph. Noting that the agency had rejected this approach, the comment requested the agency to reconsider synchronization of effective dates for interrelated ingredients to minimize the resource burden and economic impact of possible multiple reformulations and ultimately to benefit consumers.

As the comment noted, the agency previously addressed this issue in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30554, comment no. 65). The agency stated there that its policy is that an OTC drug product, whether single ingredient or combination, must conform to an applicable monograph on the effective date of the final monograph. The agency has reconsidered this issue, as the comment requested, but concludes there is no need to change its policy on cough-cold combination product reformulations. All of the final monographs for the different pharmacologic classes of OTC cough-cold ingredients have been issued and are currently effective. Therefore, most currently marketed OTC combination drug products that contain only cough-cold ingredients should now contain monograph ingredients and labeling.

A few combination products containing only cough-cold ingredients and a few cough-cold combinations that contain internal analgesic or oral health care active ingredients may need reformulation of the cough-cold component(s) covered by part 341 and § 310.545(a)(6). However, the internal analgesic or oral health care ingredient(s) in the combination product is/are not affected by this final rule. Manufacturers have 24 months to relabel combination products containing only cough-cold ingredients. The date for relabeling cough-cold combination products that contain internal analgesic or oral health care active ingredients will be specified in those final monographs.

D. Comments on Specific OTC Cough-Cold Combination Drug Products

(Comment 9) One comment stated that the table for combination drug products (53 FR 30522 at 30556 and 30557) lists analgesic-antipyretic(s) and an oral antitussive as a category I combination, while proposed § 341.40 *Permitted combinations of active ingredients* does not list this combination.

The comment believed this was an oversight, and requested that an appropriate subsection be created in proposed § 341.40 to include this combination.

The agency is correcting this oversight by amending § 341.40 to include this combination.

(Comment 10) One comment was concerned that proposed § 341.40 did not specifically provide for cough-cold combinations with buffered aspirin and requested the agency amend the appropriate paragraphs of § 341.40 to include the phrase "or buffered aspirin or aspirin and antacid combinations."

The tentative final monograph for cough-cold combination drug products was published before the internal analgesic tentative final monograph, and at that time the agency could not identify specific sections for the internal analgesic ingredients in these combinations. These sections can now be identified for all combinations that can contain buffered aspirin or aspirin and antacid combinations. Section 341.40(a), (c), (f), (g), (l), (m), (n), (o), (q), and (r) of this final monograph will be amended in the future to identify the specific section numbers for internal analgesic ingredients, including buffered aspirin and aspirin and antacid combinations, when the final monograph for OTC internal analgesic-antipyretic drug products is published in the future.

(Comment 11) One comment disagreed with the category III classification of combinations containing caffeine as a "sedative corrective" (an active ingredient specifically intended to counteract a side effect of other ingredients in the product). The comment noted that antihistamines are labeled with the warnings "May cause drowsiness" and "Use caution when operating a motor vehicle or operating machinery" (50 FR 2200 at 2208, January 15, 1985). The comment argued that caffeine should not be excluded from combinations containing an antihistamine to treat the common cold because of the double-

edged sedative effect of common cold lethargy and the ingestion of the antihistamine. Noting two products containing an antihistamine and caffeine marketed for 17 years with no complaints of drowsiness and no reports of ineffectiveness, the comment asked the agency to reclassify as category I combinations of an antihistamine and over 90 mg caffeine as a sedative corrective.

The agency disagrees with the comment. The Panel agreed with the rationale for caffeine serving as a "stimulant corrective" (the Panel's term), but placed combinations containing caffeine in category III until such "corrective" pharmacological action could be proven (41 FR 38312 at 38325). The agency concurred in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30543) and noted that no further data had been submitted to support the effectiveness of caffeine as a "sedative corrective" (the agency's term). No additional data were submitted after publication of the tentative final monograph for OTC cough-cold combination drug products. The marketing information provided by the comment regarding the two products containing both an antihistamine and caffeine that have been marketed for 17 years is supportive, but no clinical data were submitted. The agency considers the marketing information alone insufficient to justify inclusion of caffeine in a cough-cold combination to combat the drowsiness associated with antihistamine use or the "lethargy" that may accompany the common cold.

(Comment 12) One comment asked that proposed § 341.40(j), for oral antitussive active ingredients in § 341.14(a), be expanded to include topical antitussive active ingredients in § 341.14(b) in combination with any single or approved combination of topical oral anesthetic/analgesic active ingredients proposed in §§ 356.10 or 356.20 of the tentative final monograph for OTC oral

health care drug products (53 FR 2436 at 2458). The comment noted that proposed § 356.20 permits combinations of anesthetic/analgesic ingredients such as benzocaine with menthol and benzocaine with phenol and, thus, a category I topical antitussive ingredient (e.g., menthol) should also be permitted to be combined with appropriate anesthetic/analgesic ingredients such as benzocaine. The comment noted that proposed § 341.40(j) included only single oral anesthetic/analgesic ingredients and requested that oral antitussives be allowed to be combined with allowed oral anesthetic/analgesic combinations.

The Panel reviewed data relating to combination drug products containing cough-cold and oral health care active ingredients with claims for relief of sore throat (41 FR 38312 at 38325). The Panel established specific criteria for the treatment of symptoms with combination products and based its category I recommendations on whether the combination of ingredients is rational concurrent therapy for a significant and existing population. The majority of the data the Panel reviewed were for combinations containing anesthetic/ analgesic and cough-cold ingredients. The Panel determined that products containing an antitussive or a nasal decongestant combined with a topical oral anesthetic/analgesic in a lozenge dosage form are rational, identified a target population that would benefit from such products, and recommended classifying such products in category I (41 FR 38312 at 38325). The agency concurred with the Panel in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30536 and 30537).

In the rulemaking for OTC oral health care drug products, the agency proposed in § 356.26(e) and (f) to allow combinations of benzocaine with menthol or phenol in oral anesthetic/analgesic combination drug products (56

FR 48302 at 48343). Thus, the agency agrees that menthol can be combined with benzocaine and that menthol in such a combination could be an antitussive, an oral anesthetic/analgesic, or both.

In the tentative final monograph for OTC cough-cold combination drug products, the agency determined that combinations containing anesthetic/analgesic and cough-cold ingredients could be rational only if the combination drug product is in a solid dosage form so that the anesthetic/analgesic ingredient may exert its topical effect and the oral antitussive can be ingested (53 FR 30522 at 30536 and 30537). However, menthol can be used in a solid dosage form that is dissolved in the mouth to provide topical antitussive action. The agency classified camphor as category I for topical (ointment) or steam inhalant antitussive use (52 FR 30042 at 30056), but camphor as a single ingredient in § 341.14(b)(1) is limited to ointment and steam inhalation use.

Although the comment suggested revisions of § 341.40(j) only, the types of changes requested also apply to proposed § 341.40(q), (u), (w), (x), and (z) (redesignated as paragraphs (t), (w), (y), (z), and (bb), respectively), which include various combinations of an oral antitussive, and/or an anesthetic/analgesic, and/or an oral demulcent active ingredient. The agency is allowing the combinations specified in these paragraphs to be available in either a liquid (to be swallowed) or solid dosage form (to be dissolved in the mouth and swallowed) provided the antitussive is an oral (systemic) antitussive ingredient identified in § 341.13(a). (See section I.E, comment no. 18 of this document.) However, in this final monograph the agency is limiting any single topical antitussive active ingredient identified in § 341.14(b)(2) in combination drug products specified in § 341.40(k), (t), (w), (y), (z), and (bb) to a solid dosage form to be dissolved in the mouth and swallowed.

Menthol is used both as an antitussive and an oral health care anesthetic/analgesic. The agency has determined that an ingredient having multiple, concurrent uses can include that information in product labeling where appropriate (61 FR 15700, April 9, 1996). The statements of identity, indications, and warnings for concurrent use may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable (60 FR 10286 at 10290, February 23, 1995). For concurrent use of menthol, the statement of identity would be "cough suppressant/oral anesthetic" or "antitussive (cough suppressant)/oral anesthetic." Indications, warnings, and directions would be combined from § 341.74(b), (c), and (d) and § 356.52(b), (c), and (d).

The antitussive directions are 5 to 10 mg every hour as needed, while the anesthetic/analgesic directions are 2 to 20 mg every 2 hours. The agency's policy is that when there is a difference in the directions established for the individual ingredients in a combination drug product, e.g., when the time intervals or age limitations for administration of the individual ingredients differ, the directions for a combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph (53 FR 30522 at 30554). This policy also applies when an ingredient is being labeled for dual use in a single product. Under this rationale, the every 2 hours directions for anesthetic/analgesic use would be controlling. The problem arises, however, that amounts of menthol from 2 mg up to 5 mg are not monograph dosages for menthol for antitussive use. Therefore, the agency has determined that appropriate directions for menthol when labeled for both uses in a product is 5 to 10 mg every 2 hours. Interested

parties may comment on this dosage and provide data and information to support an alternate dosage, using the citizen petition procedure in § 10.30.

Based on the discussion above and in section II.E, comment no. 18 of this document, the agency is including the topical antitussive menthol in combinations specified in § 341.40(k), (t), (w), (y), (z), and (bb) of this final monograph. Menthol as a topical antitussive can only be available in a solid dosage form when combined with any topical oral anesthetic/analgesic active ingredient. For oral antitussive-anesthetic/analgesic combinations, the directions for the individual ingredients are different and the directions for the combination may not exceed any maximum dosage limits, which includes dosing intervals, for any individual ingredient.

(Comment 13) Four comments requested that a four-ingredient combination containing an analgesic-antipyretic, antitussive, expectorant, and oral nasal decongestant be included in the monograph. The comments stated that this combination is supported by the rationale underlying various two, three, and four-ingredient combinations containing these components that were proposed as category I in the tentative final monograph (53 FR 30522 at 30561). One comment requested that the combination of an analgesic-antipyretic, expectorant, and oral nasal decongestant be classified as category I based on related proposed category I combinations (53 FR 30522 at 30561).

Another comment referred to comment no. 47 of the tentative final monograph (53 FR 30522 at 30540), where the agency proposed to classify in category I a combination containing an analgesic-antipyretic, antihistamine, oral antitussive, and oral nasal decongestant. The comment stated that, because the agency considers that an expectorant can be added to an analgesic-antipyretic in order to provide a product that will reduce fever and facilitate

expulsion of bronchial secretions, and because the agency also considers that an expectorant can be added to an oral antitussive and oral nasal decongestant to control symptoms of excess bronchial and nasal secretions and cough, then it is rational to allow a combination containing an analgesic-antipyretic, oral antitussive, expectorant, and oral nasal decongestant that would not only control symptoms of excess bronchial and nasal secretions and cough, but also fever that might accompany such symptoms.

One comment submitted five studies (two prospective epidemiological studies (Refs. 10 and 11), one retrospective epidemiological study (Ref. 12), and two consumer surveys (Refs. 13 and 14)) to demonstrate that a clinically significant target population exists that would require the use of the combination of an analgesic-antipyretic, antitussive, expectorant, and nasal decongestant to relieve concurrent symptoms of the common cold. One prospective epidemiological study (Ref. 10) included 373 colds studied in 293 subjects. The study results indicated that subjects in 56 percent of the cases had dry cough, nasal congestion, and aches (i.e., sore throat, headache, or achiness) for 1 or more days of a cold, and 29 percent had the symptoms for 3 or more days.

The second prospective epidemiological study (Ref. 11) was a multisite, upper respiratory survey by 14 pediatricians in 14 cities across the United States. The study included 3,166 male and female subjects, 2 to 12 years of age, who were treated by pediatricians during the winter of 1981 to 1982. On the day of first examination by the pediatrician, 12 percent of the subjects concurrently had dry cough, nasal congestion, and symptoms that would ordinarily require an analgesic-antipyretic. While severity of symptoms was

not directly addressed, it was presumed the subjects had symptoms of sufficient severity or duration to visit a physician.

The retrospective epidemiological study (Ref. 12), previously submitted to the agency to support the combination of an analgesic-antipyretic, antihistamine, antitussive, and nasal decongestant, was discussed in the tentative final monograph for cough-cold combination drug products (53 FR 30522 at 30540 to 30541). The comment's data analysis showed symptoms of dry cough, pain, and nasal congestion (without the antihistamine symptoms) occurred concurrently in at least 31 percent of this study population. Although less than half of the subjects (42.8 percent) documented symptom severity, 27.8 percent of those subjects rated severity moderate to severe.

One consumer survey (Ref. 13) included data from telephone interviews with 322 people, 10 years of age or older, suffering from colds. At least 29.8 percent of the subjects concurrently had nasal/head congestion, pain/fever/sore throat, and cough/phlegm for 1 or more days, and 10.5 percent of the subjects had these symptoms for 3 or more days. The comment stated that the incidence of dry cough among subjects with the four concurrent symptoms remained high (25.8 percent on day 1 and 38.5 percent on day 7), while the incidence of dry cough among all subjects with colds declined (from 25.8 percent on day 1 to 12.4 percent on day 7).

The second consumer survey (Ref. 14) included 2,297 adults and 1,423 children 6 to 17 years of age. Female heads of household identified the most severe symptoms of the cold or flu sufferer. The survey showed 25 percent of adults and 15 percent of children with colds and 37 percent of adults and 36 percent of children with flu reported four concurrent symptoms of coughing, chest congestion, nasal congestion, and sore throat.

The agency has reviewed these data and other information and agrees they are adequate to include the following two combinations in this final monograph: (1) Analgesic-antipyretic, expectorant, and nasal decongestant and (2) analgesic-antipyretic, antitussive, expectorant, and nasal decongestant. The data showed there is a population with multiple cough-cold symptoms who benefit from these specific three or four ingredient combinations (Ref. 15).

(Comment 14) One comment requested category I status for the nasal decongestant combination of l-desoxyephedrine and an aromatic mixture containing camphor, menthol, bornyl acetate, and lavender oil, which did not include the ingredient methyl salicylate as proposed in § 341.40(s) (53 FR 30522 at 30546 and 30547). The comment noted consumers' concerns about salicylates and contended: (1) The deletion of methyl salicylate from the aromatic mixture does not affect to a measurable extent the effectiveness, manufacture, product stability, or safety of this product, and (2) the revised combination product is still consistent with the agency's "General Guidelines for OTC Drug Combination Products" (Ref. 16). The comment subsequently informed the agency that bornyl acetate is an inactive ingredient in the product.

The data (Ref. 17) that led to category I status for l-desoxyephedrine as a single ingredient and when combined with the aromatic mixture did not include any studies of the combination using the aromatic mixture without methyl salicylate or bornyl acetate. The combination contains 11 mg methyl salicylate and 0.2 mg bornyl acetate. The agency accepts the comment's statement that bornyl acetate is an inactive ingredient in this product because of the insignificant amount that is present. However, the agency is concerned about deletion of the 11 mg of methyl salicylate. While such a revised

combination might be consistent with the agency's general guidelines (Ref. 16), without data showing that methyl salicylate does not make a contribution to the overall nasal decongestant effectiveness of the combination, the agency has no evidence that the aromatic mixture without methyl salicylate has the same effect when combined with l-desoxyephedrine. Therefore, the agency is including the combination proposed in § 341.40(s) in this final monograph with deletion of the bornyl acetate but not with deletion of the methyl salicylate. The agency notes that the name for l-desoxyephedrine is now levmetamfetamine, and there is a compendial monograph for lavender oil (Ref. 18).

(Comment 15) One comment submitted data (Ref. 19) to support the reclassification of the combination of camphor, eucalyptus oil, and menthol from category III to category I for OTC topical/inhalant nasal decongestant use as an ointment and steam inhalant. The data included a resubmission of three clinical studies (CRD 82–10, CRD 82–09, and CRD 83–10), including a reanalysis of the data for study CRD 83–10 submitted previously, to demonstrate the individual active ingredients as nasal decongestant topical/ inhalant in a steam vaporizer. The submission also included two clinical effectiveness studies (CRD 87–25 and CRD 89–01) on the combination of camphor, eucalyptus oil, and menthol for nasal decongestant use in an ointment. The comment requested that this combination be classified as a category I topical/inhalant nasal decongestant in the same manner as previously done in the final monograph for OTC antitussive drug products (52 FR 30042 at 30056).

The agency has reviewed the data and other information (Ref. 20) and determined they are not sufficient to establish the effectiveness of the

combination of camphor, eucalyptus oil, and menthol for nasal decongestant use in an ointment or for steam inhalation. The statistical reanalysis of study CRD 83–10 submitted to support the effectiveness of the individual active ingredients for nasal decongestant use was discussed in comment no. 5 in the final monograph for OTC nasal decongestant drug products (53 FR 43386 at 43389 to 43390). The agency has determined that the conclusions reached on the single ingredients also apply to their use in combination. The latest submission contained no new information on this study. Further, study CRD 83–10 was the only study involving use of the ingredients in a hot steam vaporizer. The agency had informed the author of the comment previously of the need to consider a repeated measurement analysis should another study be done (Ref. 21). That type of data has not been provided to date. Based on a lack of adequate clinical effectiveness data, the agency is not including this combination in this final monograph.

E. Comments on Specific Dosage Forms for OTC Cough-Cold Combination Drug Products

(Comment 16) One comment requested that a combination of camphor, eucalyptus oil, and menthol be category I for antitussive use in a liquid dosage form by evaporation/inhalation at ambient temperatures. Noting the proposed category I status of the combination of camphor, eucalyptus oil, and menthol in an ointment dosage form for antitussive use (53 FR 30522 at 30547), the comment argued that inhalation of vapors by evaporation from a liquid at ambient temperature or from a topically applied ointment are comparable. The comment provided a protocol for an in vitro effectiveness study to determine whether the release of vapors from camphor, eucaplyptus oil, and menthol in a liquid dosage form by evaporation through a wick system is bioequivalent

to the release of vapors from the same ingredients in an ointment dosage form rubbed on the chest (Ref. 22).

The agency does not consider the release of vapors from a liquid dosage form by evaporation through a wick system to be comparable to the release of vapors from an ointment dosage form rubbed on the chest of the user. A liquid dosage form that remains in a stationary position and works by evaporation limits the mobility of the user to a specific distance from the container and, thus, is not comparable to the ointment dosage form. Because there are significant differences between the release of vapors from a wick system and the release of vapors from an ointment, the agency concludes that comparative in vitro studies will provide little useful information and that clinical studies are necessary to demonstrate effectiveness (Ref. 23).

(Comment 17) One comment submitted data (Ref. 24) to support monograph status for the combination of 0.2 percent pheniramine maleate and 0.5 percent phenylephrine hydrochloride in a nasal spray dosage form when labeled for relief of nasal decongestion associated with colds, sinusitis, or allergic rhinitis. Two new clinical studies (WM 440 and WM 464) were conducted to demonstrate added nasal decongestant benefit when 0.2 percent pheniramine maleate is added to a nasal spray containing 0.5 percent phenylephrine hydrochloride.

Study WM 440 was a randomized, double-blind, multiple-dose, placebo-controlled, trial involving 90 subjects with seasonal allergic rhinitis. Subjects were given either 0.5 percent phenylephrine hydrochloride and 0.2 percent pheniramine maleate in combination, 0.5 percent phenylephrine hydrochloride alone, or placebo two times daily, 4 hours apart for 2 days. (Pheniramine maleate was not studied alone.) Total nasal air flow rates were measured prior

to dosage and at timed intervals up to 8 hours. A subjective evaluation of symptoms associated with allergic rhinitis was also done at baseline and at hourly intervals. The investigator found significant carryover effects for time zero in the 2-day study and concluded that only results of day 1 were significant and that the combination was more effective than 0.5 percent phenylephrine hydrochloride alone.

Study WM 464 was a double-blind, single-dose, randomized, parallel-group, placebo-controlled, trial involving 240 subjects with upper respiratory tract infections (URTI). Subjective measurements of effectiveness were done at time intervals up to 4 hours using a "100 mm visual analog nasal congestion scale" and a "6 category nasal congestion relief rating scale." The investigator concluded the study showed that the combination drug product was more effective than either drug alone in subjects with URTI.

The agency finds the data inadequate to support monograph status (Ref. 25). Study WM 440 is deficient because it did not include a group in which 0.2 percent pheniramine maleate was given as the active ingredient. In addition, there were significant carryover effects and, because only the results of the first day were useful, the duration of the study was insufficient. An adequate, randomized, parallel study in a sufficiently large number of subjects who receive the test drug(s) for at least 3 days (preferably for the duration of the syndrome) is required to demonstrate effectiveness of this combination.

The agency does not consider study WM 464 adequate to demonstrate effectiveness because it was only a single-dose study and pheniramine maleate was not shown to be effective. For all the time/effectiveness measurement intervals up to 4 hours, pheniramine maleate alone showed an effect only at 15 minutes. The agency has determined that the dosages used in the study

should have been administered according to the proposed label directions and the study should have had a duration of at least 3 days if the product is to be indicated for URTI and at least 7 days (preferably 2 weeks or more) if the product is to be indicated for allergies.

The author of the comment submitted data to support a combination drug product consisting of both a nasal decongestant and an antihistamine, analyzed the study results for nasal decongestion and for symptoms associated with allergic rhinitis, but requested monograph status for this product only when labeled for relief of nasal congestion associated with colds, sinusitis, or allergic rhinitis. Nasal decongestant drug products can make this type of claim (§ 341.80(b)). The comment did not indicate clearly what claim(s) were proposed for the pheniramine maleate component of this product. The agency concludes that data supporting claims for an oral antihistamine, such as relief of symptoms of runny nose and watery, itchy eyes, are necessary.

(Comment 18) One comment requested that several proposed cough-cold combination formulations containing an oral nasal decongestant, oral antitussive, oral anesthetic/analgesic, and oral demulcent (53 FR 30522 at 30537) not be limited to solid dosage forms. The comment stated that, from a pharmaceutical standpoint, it is possible to formulate safe and effective drug products that combine demulcents (e.g., gelatin, glycerin, and pectin) in liquid dosage forms with other cough-cold monograph ingredients. The comment noted that the demulcent ingredients gelatin, glycerin, and pectin are permitted in lozenge or liquid dosage forms in the tentative final monograph for OTC oral health care drug products (53 FR 2436 at 2460 and 2461). The comment argued that the systemic action of cough-cold ingredients would not be adversely affected by the addition of a demulcent and that the demulcent

would be applied directly to the throat tissues when swallowed, thus, producing the intended protective effect. The comment contended that it is both rational and practical for the final monograph to include combinations of systemically acting cough-cold ingredients and a demulcent in liquid dosage forms.

The agency agrees with the comment. Nine combinations proposed in the tentative final monograph for OTC cough-cold combination drug products specify that the product be in a solid dosage form. See § 341.40(j), (p), (q), (u), (v), (w), (x), (y), and (z). Menthol as a single ingredient in § 341.14(b)(2) is limited to a solid dosage form. However, menthol as an oral anesthetic/ analgesic is not limited to solid dosage form products. If menthol were present in the above combinations as an oral anesthetic/analgesic ingredient, a liquid product would allow oral systemically acting cough-cold ingredients to be swallowed and would allow the oral anesthetic/analgesic (or demulcent, if present) to exert a topical therapeutic effect in the throat or mouth. The proposed directions for an anesthetic/analgesic or a demulcent in a liquid dosage form state that the product should be gargled, swished around in the mouth, or allowed to remain in place for at least 1 minute and then spit out (56 FR 48302 at 48343 to 48347). However, the anesthetic/analgesic or demulcent in a combination product should not be spit out so that the systemically acting cough-cold ingredients can be effective. The agency does not see any safety problems when small quantities of an anesthetic/analgesic (menthol) or a demulcent (gelatin, glycerin, and pectin), as allowed in products regulated by OTC drug monographs, are swallowed. Therefore, the agency is allowing the nine combination drug products to be in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and

swallowed), with specific directions for products with an anesthetic/analgesic and/or a demulcent in a liquid dosage form in § 341.85(d)(1) of this final monograph.

(Comment 19) One comment requested monograph status for the combination of camphor and menthol for steam inhalation antitussive use. The comment noted that in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30549) camphor and menthol individually are monograph drugs for steam inhalation use for antitussive claims (52 FR 30042, August 12, 1987); that further effectiveness data are not needed for these ingredients; and that data are needed to establish that the combination of these ingredients has some advantage over the single ingredients. The comment stated that whether camphor and menthol are delivered in a steam inhalation dosage form or an ointment dosage form, it is the inhalation of the aromatic ingredients that provides the antitussive benefits. The comment contended that steam inhalation provides a convenient dosage delivery form that is essentially identical to the ointment dosage form, which is rubbed on the chest, for consumers who want the benefits of medicated steam inhalation. The comment felt that the agency's "General Guidelines for OTC Drug Combination Products" (Ref. 16) also support the combination by stating that patient acceptance or quality of formulation can be considered criteria to demonstrate the advantage of a combination over its single ingredients.

The agency has determined that the comment did not provide sufficient information to demonstrate that the combination has some advantage over the single ingredients. As the agency stated in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30549), data are

required to establish that the combination of camphor and menthol for steam inhalation antitussive use has some advantage over the single ingredients. A long marketing history and a belief that the combination of these ingredients may contribute to consumer acceptance of this drug product do not provide adequate data to demonstrate that the combination provides some advantage over the single ingredients. This combination for steam inhalation antitussive use is not included in the final monograph.

III. The Agency's Final Conclusions on OTC Cough-Cold Combination Drug Products

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC cold, cough, allergy, bronchodilator, and antiasthmatic combination drug products are generally recognized as safe and effective and not misbranded. The agency has included 36 combinations in §§ 341.40(a) through (bb) and 341.70(a) and (b) of the monograph. This includes the combination of an antihistamine, oral antitussive, and analgesic-antipyretic, which was inadvertently not included in the proposal. All other cough-cold combination products are nonmonograph. These include, but are not limited to, the following combinations that were considered and rejected in this rulemaking: (1) Oral antitussive and debriding agent/oral wound cleanser; (2) antihistamine and debriding agent/oral wound cleanser; (3) oral antitussive and astringent; (4) antihistamine and astringent; (5) anticholinergic and expectorant; (6) antihistamine and expectorant; (7) antihistamine (if antihistamine is also a monograph antitussive, except diphenhydramine citrate and diphenhydramine hydrochloride) and oral antitussive; (8) oral antitussive (if antitussive is also a monograph antihistamine, except diphenhydramine

citrate and diphenhydramine hydrochloride) and antihistamine; (9) antihistamine and anticholinergic; (10) antihistamine and oral anesthetic/ analgesic; (11) antihistamine and oral demulcent; (12) antihistamine and nasal decongestant (administered topically as spray or drops); (13) oral antitussive and expectorant (for productive cough); (14) oral antitussive, expectorant, and oral nasal decongestant (for productive cough); (15) expectorant and oral anesthetic/analgesic; (16) expectorant and oral demulcent; (17) anticholinergic, antihistamine, and oral nasal decongestant; (18) atropine and oral nasal decongestant; (19) monograph ingredients from different pharmacologic groups if any ingredient is at less than the minimum effective dosage (unless the ingredient(s) are being used to treat the same symptom); (20) two or more ingredients at less than the minimum effective dosage and used to treat the same symptom (labeling claim) (even if the product contains monograph ingredients from different pharmacologic groups); (21) more than two active ingredients from the same pharmacologic group; (22) an antihistamine for the relief of symptoms of allergic rhinitis and an additional antihistamine which is added exclusively for sedation, and the product contains labeling which represents the additional antihistamine as a sleep-aid; (23) an antihistamine with a sleep-aid claim; (24) nonmonograph ingredients or labeling; (25) two monograph ingredients from the same pharmacologic group; (26) two monograph ingredients from the same pharmacologic group if either or both ingredients are at less than the minimum effective dosage; (27) a corrective (an active ingredient specifically intended to counteract a side effect of other ingredients in the product), e.g., caffeine, and any monograph ingredient(s); (28) phenobarbital (as a stimulant corrective); (29) several claimed active ingredients that are mixtures of volatile substances with overlapping

pharmacologic activities for which a minimum effective dosage cannot be established for one or more of the ingredients when tested alone; (30) a stimulant, e.g., caffeine (at a fully effective level), and any monograph ingredient(s); (31) caffeine (15 to 30 mg) to combat lethargy (not as a sedative corrective) and cold preparations not containing antihistamines; (32) vitamin C and monograph ingredient(s) for prevention or treatment of the common cold; (33) any vitamins with labeling claims for prevention or treatment of the common cold; (34) caffeine and ephedrine, phenylpropanolamine, or pseudoephedrine; (35) menthol, camphor, eucalyptus oil, thymol, cedar leaf oil, and nutmeg oil (myristica oil) in a suitable vehicle for steam inhalation or topical use as a nasal decongestant; (36) menthol and eucalyptus oil in a lozenge as a topical antitussive; and (37) menthol, camphor, eucalyptus oil, tincture of benzoin, and polyoxyethylene dodecanol for steam vaporizer use as an antitussive. A number of bronchodilator combination drug products were previously found nonmonograph (66 FR 49276).

The agency has made a minor revision in the indication proposed in § 341.85(b)(1) for combinations with an analgesic-antipyretic active ingredient labeled for relief of general cough-cold symptoms and/or the common cold, deleting the words "muscular aches," "associated with," and "(select one of the following: 'the common cold' or 'a cold')." This deletion is consistent with recommendations made by the Nonprescription Drugs Advisory Committee and the OTC Analgesic Subcommittee of the Arthritis Advisory Committee on September 8 and 9, 1994. The agency has concluded that labeling claims for analgesic-antipyretic ingredients (i.e., the myriad of claims in the labeling of presently marketed products and in proposed § 343.50(b)(1), (b)(2), and (b)(3)) should be simply and clearly stated in a general manner. The agency will be

discussing this subject in more detail in the rulemaking for OTC internal analgesic-antipyretic drug products in a future issue of the **Federal Register**. If any changes subsequently occur in that rulemaking, the agency will amend the current final rule accordingly. The agency has also made minor revisions in the indications in § 341.85(b)(1) and (b)(2) to put them into the new OTC drug product labeling format.

When the tentative final monograph for cough-cold combination drug products was published in 1988, proposed § 341.85(b)(4) referred to proposed § 356.55(b)(1), which was proposed on January 27, 1988 (53 FR 2436 at 2458). That section was renumbered as § 356.52(b)(1) on September 24, 1991 (56 FR 48302 at 48343). Section 341.85(b)(4) in this final rule will be amended in the future to refer to § 356.52(b), as appropriate.

The agency has revised the warnings proposed in § 341.85(c) to the new OTC drug labeling format, which has caused some changes in the way that the warning information is presented. In addition, in several instances, the agency changed a "do not take for more than 10 days" statement (internal analgesic component) to 7 days because of the antitussive or nasal decongestant component of the product, which has a 7-day limit on use. This approach for warnings is similar to that used for directions when the time intervals for individual ingredients differ.

Any drug product labeled, represented, or promoted for use as an OTC cough-cold combination drug that contains any of the ingredients listed in § 310.545(a)(6) or that is not in conformance with the monograph (part 341) may be considered a new drug within the meaning of section 201(p) of the act (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352). Such a drug product cannot be marketed for OTC cough-cold use unless

it is the subject of an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314). An appropriate citizen petition to amend the monograph may also be submitted in accord with 21 CFR 10.30 and 330.10(a)(12)(i). Any OTC cough-cold combination drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule that is not in compliance with the regulations is subject to regulatory action.

IV. Analysis of Impacts

The agency did not receive any comments in response to its request in the tentative final monograph (53 FR 30522 at 30560) for specific comment on the economic impact of this rulemaking. FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State,

local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation). The proposed rule published before the Unfunded Mandates Reform Act of 1995 was enacted.

The agency concludes that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. FDA has determined, as discussed in this section of the document, that the final rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order.

The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for the final rule, because the final rule is not expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation. The current inflation adjusted statutory threshold is about $110 million.

The purpose of this final rule is to add 36 allowable combinations and their labeling to the monograph and to declare a number of other combinations as not generally recognized as safe and effective. Most of the individual cough-cold ingredients in these combination products are already included in the monograph, and the majority of marketed OTC cough-cold combination drug products already contain the ingredient combinations included in the final monograph. Most reformulations will involve the substitution of one cough-cold ingredient for another or the reformulation of a product containing a cough-cold ingredient and an oral health care ingredient, where such a combination has not been established as safe and effective.

The agency's Drug Listing System identifies over 200 manufacturers and 300 marketers (distributors and repackers) of almost 8,300 OTC cough-cold combination drug products. Although some of these products may no longer

be marketed, it is likely that there are additional marketers and products not currently included in the agency's system. Thus, FDA estimates that approximately 10,000 products could be subject to this final rule. Manufacturers will incur the vast majority of the incremental costs attributed to this rule.

The agency is unable to determine the number of products that will require reformulation but, with few exceptions, manufacturers have known which ingredients were going to be included in this final monograph for a substantial period of time. Many manufacturers have already reformulated their products. Others may decide to drop the nonmonograph products from their product lines, either because they already produce a substitute product that complies with the monograph, or because product sales are marginal and do not justify the expense of reformulation.

The cost to reformulate a product will vary greatly depending on the nature of the change in formulation, the product, the process, and the size of the firm. Because of the large number of cough-cold ingredients available for substitution, no manufacturer should need to conduct clinical studies or change a dosage form; however, manufacturers will have to redo the validation (product, process, new supplier), conduct stability tests, and change master production records in order to ensure compliance with current good manufacturing practice. (See section 501(a)(1)(B) of the act (21 U.S.C. 351(a)(1)(B)) and 21 CFR parts 210 and 211.) The agency estimates that the cost of reformulation ranges from $100,000 to $500,000 per product, and may average about $250,000. FDA is uncertain about the number of cough-cold combination products that will be reformulated, but if 50 to 100 products were reformulated, the total cost would range from $12.5 to $25 million. These costs

may be smaller if most manufacturers elect to discontinue marketing marginal products rather than incur the expense of reformulating.

The agency points out that the need to reformulate existing products has two components in this final rule. Ten of the monograph combinations contain analgesic-antipyretic active ingredients and nine other combinations contain oral health care (oral anesthetic/analgesic or demulcent) active ingredients. The monographs for the analgesic-antipyretic and oral health care ingredients have not been finalized to date; therefore, the final rule does not require the reformulation of that component of such combinations. However, those specific combinations of cough-cold ingredient(s) with an analgesic-antipyretic or oral health care ingredient(s) that have been found unacceptable in this final rule must be reformulated (or removed from the market) by the date specified in the final rule. Consumers will benefit from reformulation because products that have not been found safe and effective will be replaced by products containing combinations of ingredients deemed safe and effective.

Some relabeling is required by this final rule. However, most of the relabeling results from the earlier final rule on the standardized content and format requirements for all OTC drug products. (See the **Federal Register** of March 17, 1999, 63 FR 13254.) This final rule contains only a few labeling changes for combination products containing only cough-cold ingredients. Manufacturers will have 24 months to relabel those products in the new OTC drug product labeling format in § 201.66 (21 CFR 201.66).

The incremental labeling costs for cough-cold combinations with an analgesic-antipyretic (proposed part 343) or oral health care active ingredient (proposed part 356) are minimal, because neither of those monographs has been completed to date. Although final monographs have not been published

for OTC internal analgesic-antipyretic or oral health care drug products, the current final rule includes some specific labeling for cough-cold combination products that contain internal analgesic-antipyretic or oral health care active ingredients. The date for relabeling cough-cold combination drug products with those ingredients will be specified in those final monographs.

The agency obtained estimates of relabeling costs for the type of changes required by this rule ranging from $2,700 to $10,000 per standard stock keeping unit (SKU) (individual products, packages, and sizes) for nationally branded products and from $500 to $1,500 per SKU for private label brands. Because nationally branded products make up only a small portion of all cough-cold combination products, FDA estimates, based on its experience, that 20 percent of the SKU's affected by this rule are branded products and 80 percent are private label products. Using the midpoints of the redesign cost ranges, the weighted average cost to relabel is $2,070 per SKU. Based on FDA estimates that 5 to 10 percent of the affected 10,000 SKU's will be relabeled, the total one-time incremental costs of relabeling would range from $1 to $2.1 million.

The final rule will not require any new reporting or recordkeeping activities. Therefore, no additional professional skills are needed. There are no other Federal rules that duplicate, overlap, or conflict with the final rule. The agency concludes that there are no significant alternatives to the final rule that would adequately provide for the safe and effective use of OTC cough-cold combination drug products.

The majority of the manufacturers, distributors, and repackers of cough-cold combination drug products subject to this final rule are considered small entities using the U.S. Small Business Administration (SBA) designations for this industry (750 employees). Because census size categories do not

correspond to the SBA designation of 750 employees, the agency figures are based on 500 employees. This final rule may have a significant impact on some small entities, especially those that need to reformulate or relabel a number of affected products. To provide assistance, FDA has taken steps to minimize the impact of relabeling costs on small entities. These steps include providing enough implementation time (24 months) to enable firms to use up existing labeling stock and to undertake the labeling changes required by this final monograph concurrently with the labeling changes required by the new OTC drug labeling format (§ 201.66). These actions will provide substantial flexibility and reduced regulatory burdens for small entities.

The agency considered but rejected several labeling alternatives: (1) A shorter or longer implementation period, and (2) an exemption from coverage for small entities. While the agency believes that consumers would benefit from having this new labeling in place as soon as possible, the agency also acknowledges that coordinating the labeling changes in this final rule with implementation of the new OTC "Drug Facts" labeling significantly reduces the costs of this final rule. Also, the 24-month compliance period will enable most manufacturers to implement the new labeling and to make the necessary manufacturing adjustments based on the seasonal nature of these cough-cold combination drug products. The agency rejected an exemption for small entities because the new labeling and revised formulations, where applicable, are also needed by consumers who purchase products marketed by those entities.

The agency has undertaken important steps to reduce the burden to small entities. Nevertheless, some entities, especially those firms that manufacture several affected products, may incur significant impacts. This economic

analysis, together with other relevant sections of this document, serves as the agency's final regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

V. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the labeling is a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

VI. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive

order and, consequently, a federalism summary impact statement is not required.

VIII. References

The following references have been placed on display in the Dockets Management Branch (see **ADDRESSES**) under Docket No. 76N–052G and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

(1) Comment No. C00223.

(2) Comment No. C00224.

(3) Comment No. C00225.

(4) Comment No. C00198.

(5) Dick, E. C., S. L. Inhorn, and L. C. Jennings, "'Field' Trial Among Human Volunteers Mimicking a 7-Day Boarding School Environment," Comment No. C00198.

(6) Letter from W. E. Gilbertson, FDA, to A. J. Iannarone, Hoffman-La Roche, Inc., coded LET105.

(7) Letter from W. E. Gilbertson, FDA, to G. F. Hoffnagle, Richardson-Vicks, Inc., coded ANS1.

(8) Letter from S. Salerno, The Procter & Gamble Co., to W. E. Gilbertson, FDA, dated July 6, 1995, in OTC Vol. 04GFM.

(9) Letter from W. E. Gilbertson, FDA, to S. Salerno, The Procter & Gamble Co., dated July 27, 1995, in OTC Vol. 04GFM.

(10) Attachment 4 in Comment No. C00218.

(11) Attachment 6 in Comment No. C00218.

(12) Attachment 8 in Comment No. C00218.

(13) Attachment 10 in Comment No. C00218.

(14) Attachment 11 in Comment No. C00218.

(15) Letter from W. E. Gilbertson, FDA, to R. A. Stolt, The Procter & Gamble Co., coded LET118.

(16) Food and Drug Administration "General Guidelines for OTC Drug Combination Products, September 1978," Docket No. 78D–0322, Dockets Management Branch.

(17) Comment No. C00111.

(18) *The United States Pharmacopeia XXI-The National Formulary XVI,* The United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1572, 1985.

(19) Comment No. C00217.

(20) Letter from W. E. Gilbertson, FDA, to R. A. Stolt, The Procter & Gamble Co., coded LET 117.

(21) Letter from W. E. Gilbertson, FDA, to E. J. Hanus, Richardson-Vicks, coded LET095.

(22) Comment No. C00191.

(23) Letter from W. E. Gilbertson, FDA, to R. B. Seymour, O'Connor Pharmaceuticals, coded LET108.

(24) Comment No. C00216.

(25) Letter from W. E. Gilbertson, FDA, to J. R. Jacobs, Whitehall Laboratories, coded ANS2.

List of Subjects in 21 CFR Part 341

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 341 is amended as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTIASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 341 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

2. Section 341.40 is added to subpart C to read as follows:

§ 341.40 Permitted combinations of active ingredients.

The following combinations are permitted provided each active ingredient is present within the dosage limits established in parts 341, 343, and 356 of this chapter and the product is labeled in accordance with §§ 341.70 or 341.85:

(a) Any single antihistamine active ingredient identified in § 341.12 may be combined with any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(b) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) provided that the product is labeled according to § 341.85.

(c) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(d) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) provided that the product is labeled according to § 341.85(c)(4). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70(a).

(e) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) and any single oral nasal decongestant active ingredient identified in § 341.20(a) provided that the product is labeled according to § 341.85(c)(4). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70(a).

(f) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85(c)(4). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70(a).

(g) Any single antihistamine active ingredient identified in § 341.12(a) through (e) and (h) through (m) may be combined with any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) and any single oral nasal decongestant active ingredient identified in § 341.20(a) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85(c)(4). Diphenhydramine citrate in §§ 341.12(f) and 341.14(a)(5) or diphenhydramine hydrochloride in §§ 341.12(g) and 341.14(a)(6) may be both the antihistamine and the antitussive active ingredient provided that the product is labeled according to § 341.70(a).

(h) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) may be combined with any single expectorant active ingredient identified in § 341.18 provided that the product is labeled according to § 341.85.

(i) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) provided that the product is labeled according to § 341.85.

(j) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single expectorant active ingredient identified in § 341.18 provided that the product is labeled according to § 341.85.

(k) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any generally recognized as safe and effective

single oral anesthetic/analgesic active ingredient, or any combination of anesthetic/analgesic active ingredients provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth. Menthol in § 341.14(b)(2) and part 356 of this chapter may be both the antitussive and the anesthetic/analgesic active ingredient provided that the product is labeled according to § 341.70(b).

(l) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(m) Any single oral antitussive active ingredient identified in § 341.14(a) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(n) Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any single expectorant active ingredient identified in § 341.18 and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen

with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(o) Any single expectorant active ingredient identified in § 341.18 may be combined with any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(p) Any single expectorant active ingredient identified in § 341.18 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) provided that the product is labeled according to § 341.85.

(q) Any single expectorant active ingredient identified in § 341.18 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(r) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any generally recognized as safe and effective single analgesic-antipyretic active ingredient, or any combination of acetaminophen with other analgesic-antipyretic active ingredients, or any aspirin and antacid combination provided that the product is labeled according to § 341.85.

(s) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient identified, or any combination of anesthetic/analgesic active ingredients provided that the

product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85.

(t) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any single antitussive active ingredient identified in § 341.14(a) or (b)(2) and any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient, or any combination of anesthetic/analgesic active ingredients provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(u) Camphor identified in § 341.14(b)(1) may be combined with menthol identified in § 341.14(b)(2) and eucalyptus oil (1.2 to 1.3 percent) provided that the product is available only in a suitable ointment vehicle and provided that the product is labeled according to § 341.85.

(v) Levmetamfetamine identified in § 341.20(b)(1) may be combined with aromatics (camphor (54 milligrams (mg)), menthol (80 mg), methyl salicylate (11 mg), and lavender oil (4 mg)) provided that the product is available only as a nasal inhaler and provided that the product is labeled according to § 341.85.

(w) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved

in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(x) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85.

(y) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(z) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient or any combination of anesthetic/analgesic active ingredients and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is

labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

(aa) Any single oral nasal decongestant active ingredient identified in § 341.20(a) may be combined with any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient or any combination of oral anesthetic/analgesic active ingredients and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85.

(bb) Any single antitussive active ingredient identified in § 341.14(a) or (b)(2) may be combined with any single oral nasal decongestant active ingredient identified in § 341.20(a) and any generally recognized as safe and effective single oral anesthetic/analgesic active ingredient identified or any combination of anesthetic/analgesic active ingredients and any generally recognized as safe and effective single oral demulcent active ingredient provided that the product is available in either a liquid (to be swallowed) or a solid dosage form (to be dissolved in the mouth and swallowed) and provided that the product is labeled according to § 341.85. If the combination contains a topical antitussive, the product must be formulated in a solid dosage form to be dissolved in the mouth.

3. Section 341.70 is amended by adding paragraph (b) to read as follows:

§ 341.70 Labeling of OTC drug products containing ingredients that are used for treating concurrent symptoms (in either a single-ingredient or combination drug product).

* * * * *

(b) *For products containing menthol identified in §§ 341.14(b)(2) and 356.12(f) of this chapter.* The product contains 5 to 10 milligrams menthol. The labeling of the product contains the established name of the drug, if any, and identifies the product as a "cough suppressant/oral anesthetic" or "antitussive (cough suppressant)/oral anesthetic." The indications shall be combined from § 341.74(b) and part 356 of this chapter. The warnings shall be combined from § 341.74(c)(1), (c)(2), and (c)(3) and part 356 of this chapter. The directions shall be: "Directions [in bold type] [bullet][1] adults and children 2 years and over: dissolve lozenge slowly in the mouth. Repeat every hour as needed or as directed by a doctor. [bullet] children under 2 years of age: ask a doctor".

4. Section 341.85 is added to subpart C to read as follows:

§ 341.85 Labeling of permitted combinations of active ingredients.

The statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs. If there is no established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (a).

[1] See § 201.66(b)(4) of this chapter for definition of bullet symbol.

(1) *For permitted combinations identified in § 341.40(a), (c), (f), (g), (l), (m), (n), (o), (q), and (r) containing an analgesic-antipyretic active ingredient.* The analgesic-antipyretic component of the product shall be identified as a "pain reliever" or "analgesic (pain reliever)." If the product is also labeled to relieve fever, then the analgesic-antipyretic component is identified as a "pain reliever-fever reducer" or "analgesic (pain reliever)-antipyretic (fever reducer)."

(2) [Reserved]

(b) *Indications.* The labeling of the product states, under the heading "Uses," the indication(s) for each ingredient in the combination, as established in the indications sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (b). Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in the applicable OTC drug monographs or listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f). (g), (l), (m), (n), (o), (q), and (r) when labeled for relief of general cough-cold symptoms and/or the common cold.*

(i) The labeling for the analgesic-antipyretic ingredients states "[bullet] temporarily relieves [bullet] minor aches and pains [bullet] headache" and "[bullet] temporarily reduces fever".

(ii) The labeling for the cough-cold ingredient(s) may follow a separate bullet(s) or may be combined with the relieves part of the indication in paragraph (b)(1)(i) of this section.

(2) *For permitted combinations containing an analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (m), (q), and (r) when labeled for relief of hay fever/allergic rhinitis and/or sinusitis symptoms.*

(i) The labeling for the analgesic-antipyretic ingredients states "[bullet] temporarily relieves [bullet] minor aches and pains [bullet] headache".

(ii) The indication(s) for the cough-cold ingredient(s) consists of the labeling for antihistamines in § 341.72(b)(1) or (b)(2) and/or nasal decongestants in § 341.80(b)(1)(ii) and/or (b)(1)(iii), as appropriate, and the labeling for any other cough-cold ingredient present in the combination. This labeling may follow a separate bullet(s) or may be combined with the indication in paragraph (b)(2)(i) of this section.

(3) *For permitted combinations containing an oral analgesic-antipyretic active ingredient identified in § 341.40(a), (c), (f), (g), (m), (q), and (r) when labeled for relief of general cough-cold symptoms and/or the common cold and for relief of hay fever/allergic rhinitis and/or sinusitis symptoms.* The labeling states both indications in paragraphs (b)(1) and (b)(2) of this section.

(4) *For permitted combinations containing an oral anesthetic-analgesic active ingredient identified in § 341.40(k), (s), (t), (z), (aa), and (bb).* The labeling for the anesthetic-analgesic ingredients in part 356 of this chapter should be used.

(5) *For permitted combinations containing camphor, menthol, and eucalyptus oil identified in § 341.40(u).* The labeling for antitussive ingredients in § 341.74(b) should be used.

(6) *For permitted combinations containing levmetamfetamine with aromatics identified in § 341.40(v).* The labeling for nasal decongestant ingredients in § 341.80(b) should be used.

(7) *Other allowable statements.* In addition to the required information identified in paragraph (b) of this section, the labeling of the combination drug product may contain any of the "other allowable statements" (if any), that are identified in the applicable OTC drug monographs, provided such statements are neither placed in direct conjunction with information required to appear in the labeling nor occupy labeling space with greater prominence or conspicuousness than the required information.

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs, unless otherwise stated in paragraph (c) of this section.

(1) *For permitted combinations containing an antitussive and an analgesic-antipyretic identified in § 341.40(f), (g), (l), and (m).* The labeling states the following warnings:

(i) *For products labeled only for adults.* The following warning should be used instead of the warnings in § 341.74(c)(1) and part 343 of this chapter: "Stop use and ask a doctor if [in bold type] [bullet] pain or cough gets worse or lasts more than 7 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur [bullet] cough comes back or occurs with rash or headache that lasts. These could be signs of a serious condition."

(ii) *For products labeled only for children under 12 years of age.* The following warning should be used instead of the warnings in § 341.74(c)(3) and

part 343 of this chapter: "Stop use and ask a doctor if [in bold type] [bullet] pain or cough gets worse or lasts more than 5 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur [bullet] cough comes back or occurs with rash or headache that lasts. These could be signs of a serious condition."

(iii) *For products labeled for both adults and for children under 12 years of age.* The following warning should be used instead of the warnings in § 341.74(c)(2) and part 343 of this chapter: "Stop use and ask a doctor if [in bold type] [bullet] pain or cough gets worse or lasts more than 5 days (children) or 7 days (adults) [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur [bullet] cough comes back or occurs with rash or headache that lasts. These could be signs of a serious condition."

(2) *For permitted combinations containing an expectorant and an analgesic-antipyretic identified in § 341.40(o).* The labeling states the following warnings:

(i) *For products labeled only for adults.* The warning in paragraph (c)(1)(i) of this section should be used instead of the warnings in § 341.78(c)(3) and part 343 of this chapter.

(ii) *For products labeled only for children under 12 years of age.* The warning in paragraph (c)(1)(ii) of this section should be used instead of the warnings in § 341.78(c)(3) and part 343 of this chapter.

(iii) *For products labeled for both adults and for children under 12 years of age.* The warning in paragraph (c)(1)(iii) of this section should be used instead of the warnings in § 341.78(c)(3) and part 343 of this chapter.

(3) *For permitted combinations containing a nasal decongestant and an analgesic-antipyretic identified in § 341.40(c), (g), (m), (n), (q), and (r).* The labeling states the following warnings:

(i) *For products labeled only for adults.* The following warning should be used instead of the warnings in § 341.80(c)(1)(i)(B) and part 343 of this chapter: "Stop use and ask a doctor if [in bold type] [bullet] pain or nasal congestion gets worse or lasts more than 7 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur".

(ii) *For products labeled for only children under 12 years of age.* The following warning should be used instead of the warnings in § 341.80(c)(1)(ii)(B) and part 343 of this chapter: "Stop use and ask a doctor if [in bold type] [bullet] pain or nasal congestion gets worse or lasts more than 5 days [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur".

(iii) *For products labeled for both adults and children under 12 years of age.* The following warning should be used instead of the warnings in § 341.80(c)(1)(iii) and part 343 of this chapter: "Stop use and ask a doctor if [in bold type] [bullet] pain or nasal congestion gets worse or lasts more than 5 days (children) or 7 days (adults) [bullet] fever gets worse or lasts more than 3 days [bullet] redness or swelling is present [bullet] new symptoms occur".

(4) *For permitted combinations containing an antihistamine combined with an oral antitussive.* The labeling states the warning "When using this product [in bold type] [bullet] may cause marked drowsiness." The word "marked" may be deleted from the warning upon petition under the provisions of § 10.30 of this chapter provided adequate data are submitted to demonstrate

that the combination product does not cause a significant increase in drowsiness as compared with each active ingredient when tested alone. The petition and the data it contains will be maintained in a permanent file for public review in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

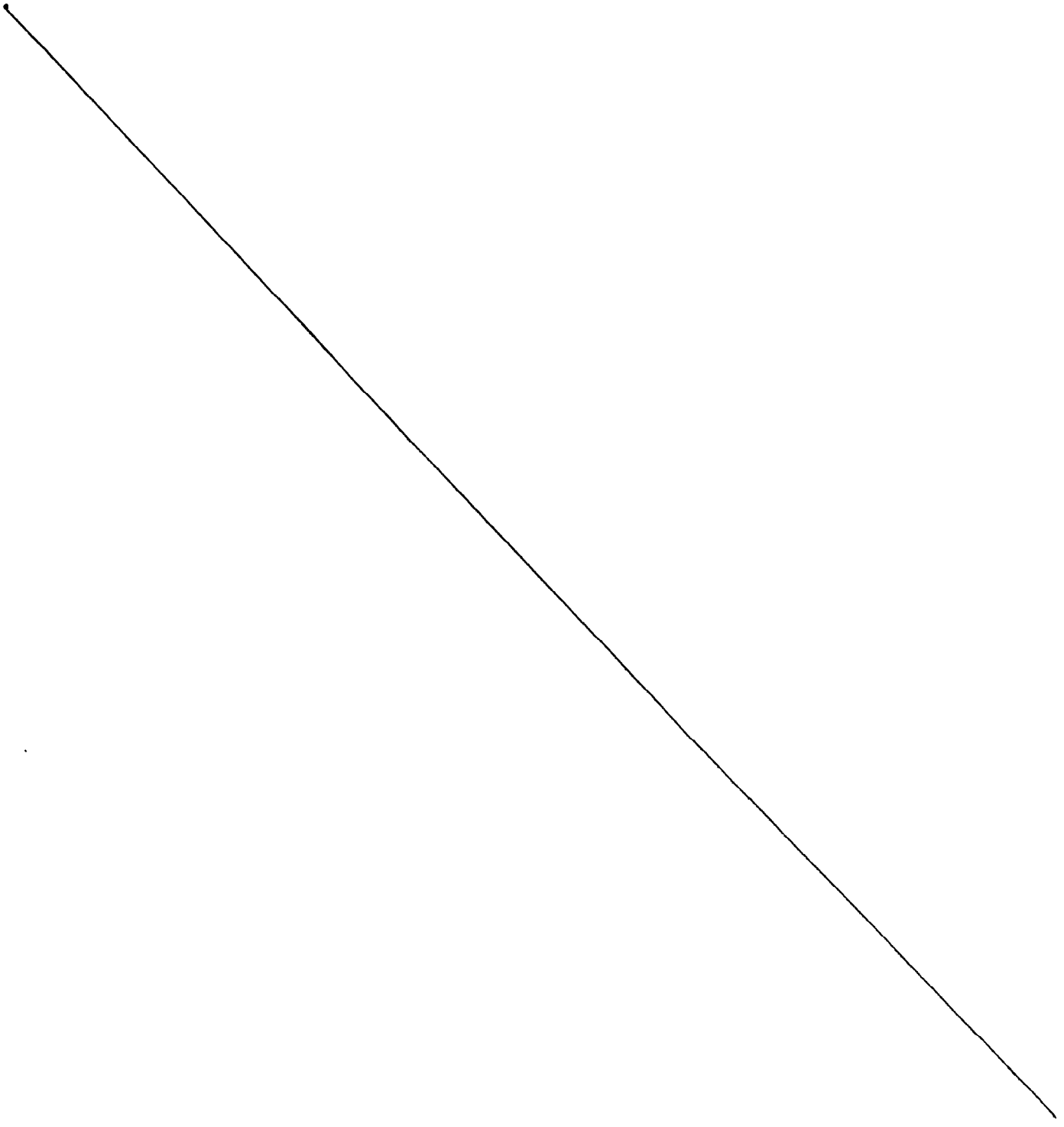
(5) *For permitted combinations containing camphor, menthol, and eucalyptus oil identified in § 341.40(u).* The labeling states the warnings for topical antitussive ingredients in § 341.74(c).

(6) *For permitted combinations containing levmetamfetamine with aromatics identified in § 341.40(v).* The labeling states the warnings for topical nasal decongestant ingredients in § 341.80(c)(2).

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs, unless otherwise stated in paragraph (d) of this section. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph.

(1) *For permitted combinations containing an anesthetic/analgesic and/or a demulcent in a liquid dosage form identified in § 341.40(k), (s), (t), (w), (x), (y), (z), (aa), and (bb).* The labeling states "[optional, bullet] gargle, swish around, or keep in the mouth for at least 1 minute and then swallow. Do not spit out."

(2) *For permitted combinations containing camphor, menthol, and eucalyptus oil identified in § 341.40(u).* The labeling states the directions for topical antitussive ingredients in § 341.74(d).



(3) *For permitted combinations containing levmetamfetamine with aromatics identified in § 341.40(v).* The labeling states the directions for topical nasal decongestant ingredients in § 341.80(d)(2)(i) and (d)(2)(viii).

Dated: 8/20/02
August 20, 2002.

Margaret M. Dotzel,
Assistant Commissioner for Policy.

[FR Doc. 02–????? Filed ??–??–02; 8:45 am]

BILLING CODE 4160–01–S